Dawkins-Noble Debate, 4 June 2022

Transcription by Jennifer Aldrich for Evolution 2.0.

Host (00:00)

...shaping how we have all understood evolution and where we come from. And since then, of course, he's written numerous other bestsellers, including The Blind Watchmaker, the God Delusion and Climbing Mount Improbable. So the opening question -- Do living organisms have functions which use genes, or do, in fact, genes use living organisms to propagate themselves? But regardless of that, I'm going to sit back and let you two take it away.
Richard Dawkins (00:29)

I approach this with some trepidation because Denis Noble was actually my doctoral examiner. <Laugh>
Host (00:38)

Richard, we're in the chair again! <Laugh>
Richard Dawkins (00:44)

So, I'm somewhat nervous. I hope I pass today. <Laugh> I would like to ask you to ignore all that was said about The Selfish Gene.
Host (00:55)

Feel free.
Richard Dawkins (00:55)

I don't know who wrote it, but anyway --
Host (00:58)

Not me.
Richard Dawkins (00:58)

-- that's not what the argument's about. To me, the argument today is about one paragraph in Denis's excellent book Dance to the Tune of Life, which is a wonderful book. Except that it's wrong.
(01:18)

The sentence, well, the paragraph concerned is: "This book will show that there are no genes for anything. Living organisms have functions, which use genes to make the molecules they need. Genes are used. They are not active causes."[1] Now I think that's a wonderful sentence because although it's wrong, it's clear. It's absolutely clear and open and articulate. And that makes my job relatively easy. Because I want to show that the exact opposite is true. The truth is opposite. Genes use individuals, use organisms as tools for their own propagation. If Denis is right, then I've been wrong for 50 years. And so have actually most of the people now working in the field, studying animals in Africa...where the kind of assumption is that organisms are working to propagate the genes that that drive them.
(02:34)

Now, I'm not saying for a moment that other things in the organism are unimportant. The rhetoric of Denis's book, I think is wonderful. I mean, it's a beautiful evocation of the unity of the organism. The fact that all the parts are working together as a system. What is wrong, however, is the view that genes are used -- in a way, he's implying that when this cell needs to make a protein, it goes into the nucleus and consult the library, which is the genome, and takes down the volume relevant to the enzyme that's needed.

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[1] This quote is from page x of the Preface to Noble, D. *Dance to the Tune of Life. Biological Relativity*. CUP 2006.

Denis Noble (03:21)

Absolutely. <laugh>
Richard Dawkins (03:22)

This is the one we need. We need to make this protein, let's get the relevant gene out and use it. That is Denis's view, he's nodding vigorously. And I have no problem with that as a physiologist, Denis is a physiologist. Or as an embryologist for that matter. That is indeed what happens. But as an evolutionist, what matters is that genes are causal agents, contradicting Denis's statement. They are not active causes. They are active causes in the following -- well, I suppose I should shut up and let...
Host (04:05)

No, finish your point...Yes, go on.
Richard Dawkins (04:09)

How do we ever recognize a cause? Well, I think the answer is this. We do an experiment. We manipulate. You cannot show that something's a cause unless you manipulate. A very trivial example -- suppose you have a hypothesis that a cock crows every time a church clock tolls. So, you observe a correlation. The clock tolls and the cock crows. Is it causal? The only way to be sure is to do an experiment. Climb up into the clock tower and change the clock, or manipulate the clock. Ideally, make the clock toll at random. And then, if the cock crows, then you've shown a causal link.
Denis Noble (05:01)

In the case of genes, we know that if you mutate a gene, then it will change the phenotype. More importantly for an evolutionist, that change will go on to the next generation and the next and the next and the next and potentially forever. Whereas if you change anything else, no matter how important it may be causally in the embryology of the animal, if you break a leg, circumcise a penis, do anything else, it will not be transmitted into future generations. And that's the crucial difference. Genes are causal in the sense that a change in a gene, a mutation, has a statistical consequence in an indefinite number of future generations.
(05:55)

Now, the reason that matters is that natural selection chooses between alternatives and the choice between alternatives only matters if it is potentially immortal, or at least if it goes on for a very large number of generations. The Neo-Darwinian theory, which Denis has a lot of criticism of in his book, is a theory of differential survival of genes in gene pools. And that only matters if the genes are potentially able to survive in the gene pool for a very long time. The ones that do survive are the ones that have a beneficial causal influence on every body in which they find themselves. Successive generations, the genes find themselves in bodies again and again. The ones that survive over many generations will be the ones that have a causal influence on a long succession of bodies. And now I'll shut up…
(06:58)

Yes, well, I love that introduction, Richard. Because 30 years ago, I did precisely that experiment. Let's go through it carefully because I think the experiment is important. This was work done with my colleague from Italy, Di Francesco. And what we discovered in that work about 30 years ago, was that a particular protein and therefore the gene -- it's an HCN protein, so it's an HCN gene -- that was responsible for the

great majority of the cardiac rhythm actually can be knocked out or the protein blocked and hardly any change in rhythm.[2]
(07:42)

Now, I'll tell you something else that I think is very important to this debate. That's what the great majority of genome sequencing and genome association studies have shown. The association levels between the cock crow and the bell, or whatever it was I've forgotten now. The association levels are actually generally, with a few outlier genes that are very clearly terribly important to the organism, they can be overridden by the rest of the organism, you see.[3] And that's exactly what was happening in our cardiac pacemaker work. What we showed is the rhythm goes like that. That's what's happening in your heart now. And it goes with a particular frequency. Let's give it 80 beats per minute. You block this particular component, which we know as a matter of physiology contributes 80% of the rhythm-generating electric current. You knock it out, there's hardly any change in frequency. Now, I think what is happening is that organisms are terribly robust. They know how to manage with whatever genes they happen to have. So what I think is happening there is simply that another network is operating. We actually have identified that network too.
(08:58)

So, we've done all of those experiments already. And I think the genome-wide association study people have done this endlessly during the period in which for, what is it now, about 20 years of genome sequencing? And what we find is that the actual association levels are quite low. And that I think is also important as a practical consequence, because that's the reason why we don't have all the medications that were promised when the first human genome sequence was announced in great fanfares on both sides of the Atlantic and around 2000 with a great Nature paper of 2001.
(09:37)

And that takes me onto another thing that I'd like to put to Richard, which is this. I think the evidence that, as you put it, the organism has gone in and changed its genes, is evident in that 2001 Nature paper on the human genome sequencing. If you all want to look it up on your mobile phones, it's Figure 42. And what Figure 42 shows is very interesting indeed. They looked at the sequences for two major groups of proteins -- the chromatins and transcription factors. And what they found was astonishing. When you look at the domains, obviously you can look at it either as a genome sequence or as protein domains that are coded for by those genome sequences. What you find is that whole domains have been pulled apart and put back together and slowly there is an accretion of these domains.
(10:38)

Now I think you, Richard, did the best calculation on this many years ago. I think it was in The Blind Watchmaker -- very good book, incidentally, I'm full of praise of your writing too. You did the calculations that show how improbably it would be that, for example, the sentence "Methinks it is like a weasel" would arise by pure chance. And what I think you did there was to show beautifully with a mathematical

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[2] These experiments are described on pages 83-89 of *Dance to the Tune of Life* (CUP 2016). The model experiment showing the robustness of the cardiac pacemaker to knock-out even of a key component is on page 118 of Noble, D. *The Music of Life*. (OUP, 2006). The full technical reference is Noble, D., Denyer, J.C., Brown, H.F. & DiFrancecso, D. 1992. Reciprocal role of the inward current, i_{bna} and i_f in controlling and stabilising the pacemaker frequency of rabbit sino-atrial node cells. *Proc Roy Soc B*, 250, 199-207. This kind of robustness has now been shown for many other physiological processes.

[3] The reference here is to the omnigenic theory that all genes are involved in some way or other with all functions: Boyle, E. A. L., Li, Y. I., & Pritchard, J. K. (2017). An expanded view of complex traits: from polygenic to omnigenic. *Cell*, 169, 1177–1186.

model, that if you held the various bits that had been shown to be correct, you would get there very quickly. And I think that's what organisms have been doing with their genes, you see. I think they do go in. Later on in the discussion, I'll explain the mechanism by which they do exactly what you are asking for. How do they go in to the nucleus and tell the nucleus what to do? I loved the way you put that, Richard. I think you are absolutely right, but probably for the wrong reasons.
Richard Dawkins (11:42)

Yes, well, now Denis, you are talking about something very interesting, which is the robustness of organisms and the ability to, as it were, manipulate and change things. And that is a wonderful fact from an embryological point of view, from an epigenetic point of view. But nevertheless, in the long run as an evolutionist, in the long run, as the generations go by, no matter how clever, even if organisms do change what effect genes have, and I'm sure they do. Nevertheless, in the long run, what matters is changes in gene frequencies in populations. And I'm talking as an evolutionist now, not as a physiologist or as an embryologist. Perhaps we could say that genes do two quite different things? In embryology what they do is influence phenotypes in highly complicated ways. Including the ways you've just enunciated. But from an evolutionary point of view, what matters is the ones that are still here 10,000 years hence. You actually use the rather vivid image, I think you said somewhere.
Denis Noble (12:59)

Yes, 10,000 years to keep a genome in a petri dish if you do nothing.
Richard Dawkins (13:01)

If you were to put a genome. Suppose somebody put Denis's genome in a Petri Dish. And keep it going for 10,000 years. Well, it wouldn't keep going. It would decay, as you rightly say. However, the information, it could be preserved on paper. You could actually write it down in a book, you could carve the ATC and G codons in granite and keep it for 10,000 years. And then in 10,000 years, type it into a sequencing machine, which we already have, and it would recreate an identical twin of Denis Noble.
Denis Noble (13:49)

I don't think it would.
Richard Dawkins (13:50)

You don't think it would?
Denis Noble (13:51)

No.
Richard Dawkins (13:52)

Why not?
Denis Noble (13:53)

Well, it would need an egg cell.
Richard Dawkins (14:00)

Oh, of course it would. In 10,000 years they will have the technology...
Denis Noble (14:08)

Oh, I see, okay. I now therefore need to follow up on a different issue then, if I may, Richard. Because you see, what you would need to be is a good self-replicator. And you won't be surprised that I disagree with you on self-replication. Because, I think it's a central feature, because I think without the self-replicator, I'm not quite sure that I understand what the selfish gene idea really means.
(14:36)

Now, let me just explain briefly why it can't be a self-replicator. The way in which that arose goes way back to the quantum mechanics, pioneer Erwin Schrödinger. Who in 1942 gave lectures in the Institute of Advanced Studies in Dublin. He published it. And what he said in that book was very insightful. It was that whatever the genetic material was, whether it was DNA, protein, or whatever, it would be found to

be a highly accurately reproduced molecular sequence. And he called that an aperiodic crystal. The word crystal matters there because you see what you say, Richard, in your books is that it replicates much as a crystal does. Now, I think that's partly true, but unfortunately not sufficiently true. Because, what exactly happens, and let's just go through it. It's got to be technical for about 20 seconds or so. What actually happens is, as we all know, the double helix discovered by Watson and Crick and Rosalind Franklin. You remember those images that were produced by -- I see all the women and a few men clapping <laugh> yes. Anyway, what Rosalind was working on, very interesting fact, was not a crystal. Her work in that critical working out of the double helix was actually on the flexible thread that actually is the DNA in a cell. You can crystallize DNA, that was done much later, but not in a living cell. Otherwise you can never read it. [4]
(16:24):

Now, why is the crystal metaphor accurate to some degree, but not to sufficient degree? And it's worth just going through the figures, because they're very important. What happens as the double helix unwinds is a C finds its mate because it naturally likes the other one that it likes to come in and link to it. And the same applies to the T and so on. So, every one of them has a mate. That's fine. Now that is a pure chemistry thing. And you could say that's almost like a crystal forming itself. Because what crystals do is that the other molecules that are in solution like to, in a lock and key fashion, go into the crystal, that's all fine. So in the same kind of way, and I think this is the reason why people like Richard say it is a self-replicator and rely on the molecular biology to say that, they're quite right, up to a point. Now, the question is, up to what point.
(17:24)

In all chemical reactions, there's an energy of formation and breakage. And from that, you know how frequently it will go wrong. In the case of the nucleotides, it's about one in 10,000 nucleotides. Now you might think that's fine. If you wrote a scientific article of 10,000 words, and you had only one word as a typo, you would be very pleased. But the trouble is, that suffices for small viruses like coronavirus, because at a mutation rate of one in 10,000, each time it's copied, would be acceptable if you've only got, say 10 or 20 or 30,000 as a genome length. We have got 3 billion. And the difference is around a million-fold. Now, how accurate is DNA replication? Obviously that first stage, which is crystal-like, and I accept the metaphor there, is accurate up to about one in 10 to the four.
(18:33)

What is the accuracy when the cell actually divides and provides two new cells? So one in 10 to the 10, hardly a single --that's rather like a proof reader of 10,000 books. Going through 10,000 books and making sure there's not a single error in the whole 10,000 books. How is that achieved? It's utterly amazing. It's achieved by the living cell. Because what then happens as the problem of the breakages, as we might call them, in the DNA formation from the double helix, when it's unwound, what then happens is the whole army of enzymes go in and literally proofread the mistakes. That's why I say you'd have to put my genome in 10,000 years hence into a living cell to do it. Now, the question is which living cell, because you see that will provide all the material initially to enable it to be reproduced. So what I'm saying is that it cannot be a faithful replicator except in the presence of its vehicle, which is the living cell. So I don't think there can be a neat separation between the replicator and the vehicle.
Richard Dawkins (19:51)

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[4] The details on why DNA cannot be a *self*-replicator are given in Noble, D. 2021. The Illusions of the Modern Synthesis. *Biosemiotics*, 14, 5-24. This article can be downloaded free on https://www.denisnoble.com/wp-content/uploads/2021/04/Noble2021_Illusions-of-MS.pdf The relevant sections entitled **Illusion 4. The Illusion of the Central Dogma.**

Proofreading is, of course, very important. And that is one of the ways in which true that self-replication happens. What matters from an evolutionary point of view is that certain genes survive in the gene pool and others don't. Now, the proofreading is very important, that helps the thing along. But what matters from the evolutionary point of view is the survival or non survival in the gene pool of successful genes versus unsuccessful genes. Successful genes are the ones which statistically have a positive effect on their own survival through gene pools. And the way they do that is via their phenotypic effects, their effects upon a succession of bodies. In any particular body, we have a combination of good genes and bad genes, successful and unsuccessful, and the body will die or not, depending upon all sorts of factors. It may get struck by lightning, it may be eaten by a lion when it wasn't looking and so on.
Denis Noble (21:03)

But on average, if a gene is successful, what that means is that it has a beneficial effect upon a large number of bodies in which it finds itself. Very often, it will find itself in the company of bad genes and it'll die anyway. But statistically on average, certain genes will get through the 10,000 year time -- more than 10,000 years, millions of years -- will get through all those generations because of its average statistical effect upon a whole lot of bodies. And others will not get through because of their average statistical effect upon a whole lot of bodies. That is natural selection. That is why animals are so good at what they do. It's why birds are so good at flying. It's why moles are so good at digging. It's why fish are so good at swimming. It's because of the average statistical effects of a whole lot of genes working together in concert with one another to make good phenotypes. And so, all the complications of what's going on inside the body, in embryology, all the proofreading, all the interactions, all the things that Denis describes so wonderfully in his book, are completely irrelevant if what you care about is the survival over many generations of certain genes rather than other genes.
(22:39)

Yes, I fully understand what you are saying, Richard, but I don't think you really answered my point because you see, I was saying that none of that would happen without the cooperation at the least, and I would say the very active cooperation of the living cell. Because as I said, it's only a living cell that can reproduce accurately. Now, I think what we need to do here is to get another element into this, because I think what you are really worried about is how can it be the body can actually change the genome. And that's the big question. Now, the reason we know that it can is we know it controls it. That's the first step. So let's see, first of all, how that can be done.
(23:26)

I've two very important colleagues have done the work I'm going to describe, so I'm going to credit them. Dick Tsien worked with me as a graduate student way back in the 1960s and is now working at the University of New York and has done part of the experiments I'm going to describe. And Anant Parekh who is a physiologist in the same department as me in Oxford. And what they've done is absolutely beautiful. They've asked the question, it's the relevant question that I think Richard is asking, how can it be that the surface of the body or of a cell -- it might be that it's a unicellular organism, then it would be the surface of the organism -- how can it know, how can its nucleus know that there is a need to change? And we now know how that can be done.[5]
(24:20)

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[5] The references are:

Ma, H., Groth, R. D., Cohen, S. M., Emery, J. F., Li, B., Hoedt, E., et al. (2014). γCaMKII shuttles Ca^{2+}/CaM to the nucleus to trigger CREB phosphorylation and gene expression. *Cell*, *159*, 281–294.

Kar, P., Mirams, G. R., Christian, H. C., & Parekh, A. B. (2016). Control of NFAT isoform activation and NFAT-dependent gene expression through two coincident and spatially segregated intracellular Ca^{2+} signals. Molecular Cell, 64, 746–759.

What they've shown is best described by imagining that a single nucleotide is about the size of my fist, and it's situated in the nucleus. So let's put that in the center of the cell. If we did that, on that scale, the surface membrane of that cell would be way up in Scotland. How on earth can it be that a signal through a receptor on the surface can influence the nucleus? And we now know how that can be done.
(24:58)

What they both found, doing different experiments and different cells, was that calcium coming through protein channels in that surface membrane using the same metaphor way, way up there in Scotland, creates a calcium concentration in a small sub space underneath the membrane. And that high calcium triggers a chemical reaction that produces a messenger. And that messenger gets attached to some extremely important proteins in the cell. Those proteins are called tubulins and the name suggests what they do -- they form tubes, literally. There are tube trains in cells. And, I'm not joking, because what happens is those tubulins run all the way through, from one edge of the cell to another. They have little motors on them, little molecular motors, and they can attach a messenger molecule to the motor.
(25:57)

And what then happens is phenomenal. They literally walk along the tubulin. It takes just a few seconds to go from that surface -- imagine on this scale, way up there in Scotland -- to the nucleus. What does it do? In those experiments it changes the gene expression levels in the relevant genes that matter for that particular function.
(26:21)

Now, the only thing that's missing here, and I'm sure Richard will pick this up very quickly so I'll say it myself, is that those are very recent experiments done 2016 and more recently, 2018 I think it was. The important point is that we don't yet know how that induces genome change. And I really mean actual change in DNA. And yet we know also that those processes must be able to do that because we can show that. Let's take a tumor developing in your body. And it's a bad situation. You're beginning to get metastasis. So the doctors get out the radiotherapy and the chemotherapy, they attack it and try to destroy it. What happens? The tumor cells themselves tell the genome to increase the mutation rate. How can they do that? Precisely by the kinds of mechanism I just described. Because the mutation rate is under the control of what is happening in their body as a whole. What then happens is phenomenal.
(27:34)

It happens in your immune system all the time. It happens in bacteria all the time because they change their genomes in response to antibiotics. And what they do is very simple. You remember that difference between one in 10 to the four and one in 10 to the 10. That depends, as I said, on the cell, having these repair mechanisms, the proofread mechanisms, but you see, they can be downregulated. That process can be downregulated. And what that does is to produce literally millions of new DNA sequences that can then be selected. Now, selection, and I agree there is a kind of natural selection here within the organism. Now, the question is very simple. Do those new sequences get to the germ line? You bet they do.
(28:23)

And that, I'm afraid, is where I think the big hole in the theory lies. Because, once you can do that, you can get what, for example, Zhang and his colleagues have shown in a paper published in 2018.[6] I can send all these references to anybody who sends me an email. So if you're worried about whether I'm

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[6] The reference is:
Zhang Y, Zhang X, Shi J. et al. (2018). Dnmt2 mediates intergenerational transmission of paternally acquired metabolic disorders through sperm small non-coding RNAs. *Nat. Cell Biol*. 20, 535–540. https://doi.org/10.1038/s41556-018-0087-2

telling the truth, just send an email and I will send you the reference. What they showed was that a small non-coding RNA, that's a little bit of technology, but a new sequence generated by the organism, can pass to the germ line cells, which become eventually of course, the eggs and the sperm. And what that will do is then tell the next generation to inherit the metabolic characteristics that were conveyed by that. I'm sorry to say this, because I know this is a dirty word amongst most evolutionary biologists, but Lamarck is back, very simple.
Richard Dawkins (29:22)

By the way, the walking mechanism is simply beautiful...absolutely uncanny. At one point, Denis, I thought you were confusing gene expression, which of course is obvious...
Denis Noble (29:39)

...that's why I went on to explain how those changes can then be communicated.
Richard Dawkins (29:51)

That's an extremely important distinction. There's no dispute, whatever about certain genes being turned on in some cells and others in other cells. That's what embryology is all about. However, what Denis went on to say is that there's evidence that it actually gets into the germ line.
Denis Noble (30:08)

Yes, that's right.
Richard Dawkins (30:09)

And Lamarck is back. Well, if Lamarck is back for an indefinite number of generations, I'm impressed. If it's only for a couple of generations, I'm not. But let's suppose that it is for a larger number of generations. If that's true, then I would have to revise what I say to include any change in the germ line. Then now becomes admitted into the charm circle of replicators. And that's fine. I doubt it. But I don't want to be dogmatic about saying that the DNA in the existing germ line is all there ever was, if on some other planet and maybe on this planet, it's true the germ line can be altered, then that's fine. The broad church of the selfish gene can embrace that. <Laugh> As I say, I doubt it.
Denis Noble (31:16)

Okay, yes. But look, Richard, I think the one thing to perhaps make clear to the audience is this is happening in everybody in this room. Because, we had the pandemic that arrived with coronavirus. Now, of course, we've fortunately developed vaccines against the virus. And that's been our great saving grace. But what would've happened anyway, with a lot of people dying, of course, would've been that our immune systems would've done exactly what we are describing. That is, they would've used that mechanism for hyper mutating, that is mutating extremely quickly, to produce millions of new DNA sequences. And then that is used to be what then gives you the acquired immunity, obviously.
(32:05)

Now what Richard is questioning is, okay, maybe that can occasionally be passed to the germ line, we don't know that yet, whether an immune response can be passed to the germ line. And I would readily say, we don't know that yet. But what is important is Rich's point about how temporary it is. Now, it's very important, indeed, and I agree with Richard about the importance of temporariness or permanence. Because it seems to me that what these mechanisms give is the option for the evolutionary process to try it out. If there's an environmental change that makes it very difficult to survive, and all organisms are under stress, and they alter their genomes and pass some of that even temporarily onto the next generations, what the next generations can do is to find out whether they do experience that change in environment or not. If they don't, then it's great that it's temporary. You don't have to alter the main genome. If it is, more or less, permanent and goes on for many generations, then how can it get assimilated in the genome?
(33:19)

Conrad Waddington showed how to do that way back in the 1950s. Incidentally, his book, The Strategy of the Genes, has been rightly republished in 2014. So, you can buy it again, it was published in 1957. He did beautiful experiments on fruit flies. He induced changes with very tiny gentle persuasions from either heat or ether or some other experimental techniques in which he could persuade a few of the flies to show a new characteristic. And he actually determined how many generations would you have to continue to do that in order for it to become assimilated into the genome? It's about 14. Not very long. What he was showing is what he called genetic assimilation. I think it was a great mistake that Waddington was ignored by the evolutionary biologists, and that's a shame.
Richard Dawkins (34:16)

The Waddington effect was actually selection.
Denis Noble (34:20)

By him.
Richard Dawkins (34:22)

Well, the flies that didn't respond correctly to the heat shock died.
Denis Noble (34:29)

Yes, that's right.
Richard Dawkins (34:30)

And so it was selection. It was Darwinian.
Denis Noble (34:32)

I'm agreeing with you.
Richard Dawkins (34:33)

It only looked like Lamarckian.
Denis Noble (34:35)

This may be the only point in the evening where we totally agree. That was selection. Yes, I absolutely agree. I agree with you. What Waddington was doing was a simulation of a Lamarckian experiment for quite a different reason. And I think it comes back to your opening question to me: Do you still hold to the idea that it's agency that organisms have rather than DNA? Now I do, because you see, I think what organisms are doing is partly through their social choices, effectively choosing which genes they will allow to survive. That's what Waddington is doing too.
(35:11)

Social selection. Yes.
Richard Dawkins (35:15)

How?
Denis Noble (35:16)

Well, who you mate with, for example. We're back to Darwin's idea of sexual selection....
Richard Dawkins (35:25)

So, why drag Lamarck in then?
Denis Noble (35:27)

I think that's Lamarckian because it's part of the use within the social context. What Lamarck was insisting on was the idea that use and disuse was itself something that could be inherited. And I think this is something, of course it starts culturally, but it becomes something that can be inherited through the fact that you are as organisms choosing the characteristics that you want to survive in the later generations. Why do we marry anybody? Isn't that why we do it? <Laugh>
Richard Dawkins (36:03)

But Denis, I mean, this is perfectly Darwinian what you're talking about.

Denis Noble (36:09)

Yes, absolutely, I agree. And Darwin was a Lamarckian. I'm not joking.
Richard Dawkins (35:16)

No, you're not.
Denis Noble (36:18)

No. In 1868, he published his theory of gemmules, which is precisely the thing we've now discovered as the extracellular vehicles today. So I absolutely totally agree with you, Richard. Darwin was indeed a Lamarckian. I'm a good Darwinian.
Richard Dawkins (36:35)

You're a sixth edition Darwinian. <Laugh> Darwin in the sixth edition of the origin species did flirt with Lamarckism, that is true. That's a historical fact. But it's not a very important biological fact.
Denis Noble (36:50)

Oh, I think it's extremely important.
Richard Dawkins (36:53)

Okay, well.
Denis Noble (36:55)

No, seriously Richard. Because he collaborated with -- this is not very well known -- he collaborated with physiologists in the last 20 years of his life. Between 1872 and 1882, he collaborated with my predecessor as the chair of physiology Burdon Sanderson, and he collaborated with his student George Ramones in a very simple set of experiments. Because you see, he took Lamarckism so seriously that he invented this theory of gemmules. And I better, just briefly, explain what that is. He realized, as Richard has beautifully explained, that you've got to explain how it can be that the body can, in its changes, due to use and disuse, communicate any of that to the germ line. Otherwise, all of that information, as Richard beautifully expressed <inaudible> would be lost. So how can that be communicated? He couldn't see what could possibly do that. So he invented an idea, and he admitted it was an idea. Which was, that tiny particles put out by the cells themselves, which he called gemmules, would be able perhaps to pass through the bloodstream down to the germ line. That was his way of explaining the soma to germ line expression. But he readily admitted at the time, this was just a hypothesis, because he couldn't see them. Now with 19th century microscopy, indeed you could not.
(38:18)

The 20th century microscopy, and 21st century microscopy even better, we've been able to do so. The experiments are simply beautiful. Just go online and ask to look at extracellular vesicles made evident by labeling molecules fluorescently, so they literally glow green, yellow, red, or whatever it might be. It enables you to know this is this particular RNA, this is this particular DNA and so on. And that escapes the limits of light microscopy. You can actually resolve down to very tiny particles indeed. They're called extracellular vesicles. Those have been shown experimentally to be passed to the germ line. That's how the RNAs and DNAs, the new RNAs and DNAs get to the germ line.
(39:10)

So, if he was alive today, I think Charles Darwin would be praising and cheering the discovery of extracellular vesicles. They are his gemmules, and they carry out the function that Darwin proposed. Now, why did he spend the last 20 years of his life collaborating with George Ramones is because he actually thought this must be right. So I don't think it's trivial that Darwin was a Lamarckian.
Richard Dawkins (39:38)

Okay, I do think this is actually quite misleading. What Darwin's gemmules was supposed to be about was investigating the current state of the body and passing it on to the next generation. So the gemmules were going all around the body and they were detecting changes in the body. The sort of

classic Lamarckian examples like the blacksmiths' arms getting muscular and the giraffes' neck stretching and things like that. Lamarck thought that those were inherited. Darwin in his later years, thought they were too. And Darwin's gemmules were going around the body in the bloodstream and picking up information about the current state of the body, the modified state of the body, the acquired state of the body. And going to the germ line, going to the gonads and imprinting the information into the germ line. Now, that is a very radical idea.
Denis Noble (40:39)

It's precisely what the extracellular vesicles are doing.
Richard Dawkins (40:42)

Well, yes, but they're not. It's nothing to do with the blacksmith's arms. They may be doing something if you are right about the immune system. You seem to be suggesting that what happens is that when the immune system reacts to an infection like COVID, and we become immune to it, that immunity gets passed on.
Denis Noble (41:08)

No, I deliberately said we're not yet sure about that.
Richard Dawkins (41:11)

I know you did. And I'm glad you said that.
Denis Noble (41:13)

But what we are sure about is that other things are passed on. Metabolic disorders are passed on and sexual preference are passed on....
Richard Dawkins (41:22)

Sexual preference is in what way passed on?
Denis Noble (41:25)

It's passed on in planarians and that's been demonstrated, -- again, all of these references, I'm very happy for people to email me and ask for them -- but that's been shown very recently by Toker and his collaborators' work in Israel. And I think that is actually a 2021 reference.[7]
Richard Dawkins (41:42)

And how many generations?
Denis Noble (41:45)

Well, what they're showing -- okay, come back to the point I made about temporary and permanent. Because you see, temporary is actually an advantage if you don't yet know from an evolutionary perspective whether the change is valuable or not. I think it's great that epigenetic changes and temporary alterations of the germ line are not necessarily passed on through many, many thousands of generations. Because if the change in the environment is really temporary, you don't want a permanent response. So I can see the evolutionary logic of doing it in that kind of way. You keep it soft until it needs to become hard. And then you let it become hard. You let it then become assimilated into the genome.
Richard Dawkins (42:35)

Well, that's fine. That's coming back to the Waddington effect in a way.
Denis Noble (42:39)

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[7] The reference is:
Toker, I.A., Lev, I., Mor, Y., Gurevich, Y., Fisher, D., Houri-Zeevi, L., Antonova, O., Doron, H., Snava, S., Gingold, H., Hadany, L., Shaha, S., Rechavi, O. (2022). Transgenerational inheritance of sexual attractiveness via small RNAs enhances evolvability in C. Elegans. *Developmental Cell*, 57, 298–309. https://doi.org/10.1016/j.devcel.2022.01.005

To some extent, Richard. Yes, this is why I said that Waddington was badly ignored.
Richard Dawkins (42:45)

Or sometimes called the Baldwin effect.
Denis Noble (42:48)

Sometimes called that, yes. But I think what's happened today is that we actually now know the precise mechanisms by which it can happen. We know the molecular biology, we know the cellular biology of it. So what I'm saying is, it's time for evolutionary biology to catch up.
Host (43:07)

If I may ask in that case, how long would it need to be? You've asked a few times. I'm really taken by this sort temporal thing. How long would it need to be to have an effect, do you think?
Richard Dawkins (43:18)

In order to be evolutionarily interesting then it needs to be something that we see as a change in the gene pool. A change in the gene pool would be, I can't put an actual number of generations on it, but it's not a proper Darwinian change if it's just -- for example, there's evidence that starvation effects can...
Host (43:47)

I was going to ask about that next, yes.
Richard Dawkins (43:49)

...epigenetic effects are, as the embryo develops, changes in the expression of genes in different parts of the body. So, in liver cells, certain genes are turned on, in kidneys cells, other genes are turned on, in muscle cells, other genes are turned on. Those are epigenetic effects. Now, there is some evidence that those epigenetic changes can be inherited into the next generation and possibly the grandchild generation. That's not a proper gene pool change.
Denis Noble (44:27)

Yeah, I think Richard is right on that. But what we would need to do is to look at the effects after billions of years. And that's exactly what the human genome project did in its Nature paper of 2001. Remember, I referred to Figure 42 of that paper. You see there the evidence that those genomes were changed by moving great chunks around in the genome. There's not time, I guess, to go through the detail of that. That's fairly clear evidence that it must have happened during evolutionary time scale. [8]
Host (45:01)

Fascinating. As we are approaching the question portion of this, I'm sorry to cut you off, Richard. It's obviously also important to say that increasingly with modern technologies, people are starting to look at the genomes of other humanoid species. And looking into the past to get more information on perhaps what our more recent ancestors look like. And it might be quite interesting to see whether or not those pieces of data can add to this conversation in due course.
Richard Dawkins (45:35)

What bothers me is Denis is saying Lamarck is back. Because in order for Lamarck to be back, we would need to have something more like the blacksmiths' arms effect. Where an adaptation - and there's plenty of adaptations that happen in a lifetime. Your muscles develop when you use them. It will be wonderful, maybe on some other planet, it happens that when your muscles develop -- you get a sun tan when you -- all sorts of adaptive changes like that get inherited. That's what Lamarck was suggesting. And I think to say that Lamarck is back is going give a misleading impression because people will think you are saying that something like the giraffe effect, the blacksmith effect.

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[8] This figure from the Lander et al Nature 2001 article is reproduced as Figure 7.4, on page 202 of *Dance to the Tune of Life. Biological Relativity* (CUP, 2016). The explanation is on pages 201-204. The original *Nature* article is Lander et al 2001/ Initial Sequencing and Analysis the human genome. *Nature*, 409, 860-921.

Denis Noble (46:20)

I think to be very precise, it is that the inheritance of use and disuse is now evident. That's the way I would put it.

Richard Dawkins (46:28)

Well, yes, is it? You're not going to go out and say that adaptation, as we see it in the field, as animals develop camouflage, as animals develop stronger bones as they use them, stronger muscles as they use them, that would be a proper Lamarckian effect. That would be a real adaptive change as a consequence of use and disuse.

Denis Noble (46:53)

And we know that the RNAs that communicate all of that can be transmitted to the germ line. So we've got part of the evidence that obviously...what I would want to say on this is this is open field for experimentation in the future. That's what we need. We need to be open to those possibilities.

Host (47:12)

Oh my gosh, I'm in the unenviable position of having to open this conversation up to more questions from the floor. So, if you'd like to raise your hands and throw your questions into the mix....

Gentleman 1 (47:32)

Thank you both for an incredibly stimulating conversation. One of the things that we haven't really addressed in this, and probably it would take an entire session. Professor Dawkins, you've repeatedly said that modifications don't get into the germ line. Obviously, at some point they do insofar as, for instance, to take one example, we had ancestors common with chimpanzees, and at some point they had offspring with germ lines which were distinctly different. Which led to human beings. And other offspring from that same species of ancestor that developed into chimpanzees. Not quite as different as we had expected until we did the detailed DNA sequencing, but nonetheless, distinctly different. Could either of you say anything about how those modifications might have happened?

Richard Dawkins (48:52)

Well, that's just standard Darwinian natural selection. There was a common ancestor 6 million years ago, and it had two children. One of those children was destined to become our line and one was destined to become the chimpanzee line. And they just evolved in different directions.

Gentleman 1 (49:12)

How did their germ lines change?

Richard Dawkins (49:15)

By natural selection -- mutation and selection.

Denis Noble (49:18)

Yes, but I think what you're getting at, if I've interpreted you correctly, is could there be a role for the organisms themselves in that? And I think there could be. Because, come back to Waddington, one of the things that he realized is that -- and we're back to the experiment that I did on heart frequency all of those years ago. The networks of organization within organisms are capable of flipping. They have different successful states in which survival can be assured. And that's what we are finding, in effect, the robustness lies in the fact that there are many such states. And that is what can then, by the mechanisms I've described, be communicated to the germ line. It may be a simple flip to come back to your question that enabled one lot to go one way, another lot the other way. And Waddington shows that with these little valleys that he does in his landscape diagrams. So I think you're basically right in your instinct. There could have been that kind of flip of the system above the genome. That's why my book, The Music of Life, is called "biology beyond the genome," because I totally subscribe to that idea.

Richard Dawkins (50:39)

But that could have been said of any split, not just chimpanzees. You could have asked any split you like in the whole history of life and Denis could have given the answer he's just given. And I could have given the answer I've just given.
Gentleman 2 (50:58)

Thank you for a wonderful debate. Professor Dawkins, I want to follow up on something you just said and connect it to something you said earlier. Because you said that over many, many, many generations there's a gene pool. And if we look at that pool, we can see what survives and what doesn't. And clearly that's the case. But there are also other pools. There are pools for example, of the proteins that correct genomes. There's pools of the salts. There's pools of the components for cellular building blocks. I think to rephrase what Professor Noble was saying, all of these different pools interact at different levels. And so why the exclusive focus on the gene pool, as opposed to the pools of all of the other cellular components as being relevant for evolutionary history?
Richard Dawkins (51:48)

Because the genes are self-replicating.
Gentleman 2 (51:51)

But not without those other molecules.
Richard Dawkins (51:53)

Not without them, they need them, of course they do. It's very important that they have all the machinery of self-replication.
Gentleman 2 (51:59)

So why don't we talk about the machinery of self-replication pool?
Richard Dawkins (52:02)

We do talk about it. It's got to be there. But nevertheless, the information that gets passed down the generations is DNA information.
Host (52:13)

I have to jump in. I'm also a biologist, I should have disclaimed this at the beginning. I tend to think of this as, unfortunately, a bit like leader bias in companies. There would've been no Apple without Steve Jobs, the idea kind of thing. You need the people to do the work, but without the concept, without the leader, without the gene to give the information and pass the plan on ,the rest is moot almost. Not to sound too hierarchical.
Gentleman 3 (52:54)

Can I just ask you, Richard, what would be necessary for you to agree with Denis? Denis has given us examples of acquired characteristics. You <inaudible> them by talking about the blacksmiths' arm. That parody was not helpful because we have seen acquired characteristics from Denis. I want to know what kind of acquired characteristics would lead you to change your mind and agree with Denis?
Richard Dawkins (53:31)

Well, the other half of the Lamarckian theory is use and disuse. Lamarck thought that if you used a bit of yourself a lot, it would grow. And that's true of muscles and one or two other things. That is quite inadequate to explain the highly complicated adaptations, such as eyes and ears. Eyes don't get better because they're used. Lenses don't get clearer because photons wash through them. That would be a kind of use and disuse Lamarckian effect. It only works for a tiny minority of things like muscles. And it may work for some of the things Denis has been talking about. But it's not an explanation for the beauty of the elegance of life. The fact that living things also have this wonderful illusion of design. For that, you need proper Darwinian natural selection.
Denis Noble (54:31)

Well, I obviously disagree with that way of looking at... We're not getting to the point of an agreement. I think the problem here is, what in the evolutionary process have we been able to identify as epigenetic and communicated to the germ line, and which is purely genetic? Now, there's been a beautiful study of that, believe it or not, on Darwin's finches. Because the experiments I'm going to describe are based on looking at the evolution of Darwin's finches. What they did was to look at the various finch species, and plot the epigenetic changes as the species diverge on the tree of life as normally drawn. And how did that correlate with the genetic changes? And the correlation is almost perfect. But what that means, and I've put to Skinner, the person who did these experiments with his team, I put the question, Do you know, which was initiating this? And he said, Well, you'll never know because they interact and that's your problem. So how do you know whether something was initiated by an epigenetic change or by a genetic change? And that's the difficulty we face, I think. So I'm not sure that we could easily determine what are the relevant, relative contributions of epigenetic and genetic change.
Richard Dawkins (56:15)

Epigenetic just means gene expression.
Denis Noble (56:17)

No, no, no... It means the changes in marking that can change gene expression, but they're also inherited. So that's the problem. And those markers are inherited. We once thought they were all wiped, clean. That's no longer true.
Host (56:36)

That is not true.
Gentleman 4 (56:40)

Sorry if my science is a bit rusty, it's been a long time since I've done any serious scientific work. It's really fascinating, Professor Noble, what you've talked about and the mechanisms you've discussed. It sounds though like what you're talking about are a series of mechanisms to control and change the rate at which DNA mutations take place and are passed on. And that's amazing and fascinating, and it would be a novel new mechanism, if and when you prove it. But the tone of the debate has been more like, genes are not the main organizers of what's happening, and the organism itself is, in fact, taking precedence. Whereas it sounds to me like even when that's shown, it's a genetic mechanism, it's a set of genes that control for a mechanism, which alters the DNA. And it sounds like that you'd still have all your work ahead of you to show that in fact organisms are the dominant force there. I could...envisage a set of circumstances in which it was disadvantageous for an organism to be able to control its own genes. Say, if something in the environment could fool it into doing it badly, and we might see that mechanism fade away.
Host (58:13)

If you can answer very, very quickly, Denis.
Denis Noble (58:19)

I'm a computer programmer amongst other things, that's how I did the mathematical models of the heart all those years ago. I cannot find, nor can anybody else find a program in the genome. That's my answer.
Host (58:33)

Thank you. On that delightful note, please can we take a moment to appreciate the civility and eloquence with which these two gentlemen have debated and disagreed this moment?
Richard Dawkins (58:45)

Could you sign my book, Denis?
Host (58:47)

Oh my gosh, look at this...and that is how it's done.